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Extracorporeal membrane oxygenation without invasive mechanical ventilation for acute respiratory distress syndrome: an international cohort study

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Abstract

Rationale: In acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) without invasive mechanical ventilation (IMV) is particularly challenging.
Objectives: To study ARDS patients treated with ECMO to avoid IMV (primary awake ECMO) or with extubation during ECMO support (extubated ECMO).
Methods: International retrospective cohort of adult ARDS patients treated with ECMO without IMV at 14 centers in 8 countries (2015-2024). The primary outcome was mortality 90 days after ECMO initiation.
Measurements and Main Results: Among 307 adult patients with ARDS, 113 received primary awake ECMO, and 194 were extubated on ECMO. Ninety-day mortality was 30.1% in the primary awake ECMO group and 14.9% in the extubated ECMO. Strategy failure occurred in 46 (40.7%) patients and 47 (24.2%) patients, respectively, most frequently within the first 10 days. In multivariate analysis, strategy failure was associated with 90-day mortality (hazard ratio [HR] = 7.67; 95% CI, 3.44-17.11; $P < .001$ in extubated ECMO; HR = 5.95; 95% CI, 2.63-13.46; $P < .001$ in primary awake ECMO), while higher age and longer time from ICU

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admission to ECMO cannulation were associated with 90-day mortality in extubated ECMO and primary awake ECMO, respectively. The leading cause of strategy failure was worsening of respiratory failure, followed by agitation/delirium in primary awake ECMO and inability to clear secretions in extubated ECMO

Conclusions: Patients selected for primary awake ECMO and extubated ECMO presented different baseline characteristics, strategy failure, and 90-day mortality rates. However, strategy failure was consistently associated with 90-day mortality in both groups.

Keywords acute respiratory distress syndrome, extracorporeal membrane oxygenation, extubation, invasive mechanical ventilation, spontaneous breathing

At a Glance Commentary

Scientific Knowledge on the Subject

- In acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) without invasive mechanical ventilation (IMV) is particularly challenging and not well studied.

What This Study Adds to the Field

- Our multicenter, international study is the largest cohort of ECMO without IMV for ARDS and included 307 adult patients from 14 centers in 8 countries using 2 distinct strategies: ECMO to avoid IMV (n = 113) and extubation during ECMO (n = 194).
- Patients selected for ECMO to avoid IMV presented distinct baseline characteristics compared to those extubated during ECMO, with higher strategy failure (40.7% vs 24.2%, respectively) and 90-day mortality (30.1% and 14.9%, respectively).

Introduction

In acute respiratory distress syndrome (ARDS), the use of venovenous extracorporeal membrane oxygenation (ECMO) without invasive mechanical ventilation (IMV) remains particularly challenging and poorly studied. Available data are limited to individual case reports and small case series.[1-6] Notably, this approach often conflates 2 distinct strategies that likely involve different patient populations and outcomes. It is essential to differentiate between primary awake ECMO (ECMO-PrAw), where ECMO is initiated to avoid IMV altogether, and extubated ECMO (ECMO-Ext), where patients are extubated during ECMO support.

In a recent Extracorporeal Life Support Organization registry analysis, ECMO-PrAw was performed in only 2.8% of patients with ECMO for acute respiratory failure.[7] In a survey that included 253 ECMO centers worldwide, less than one-third reported performing ECMO-Ext in acute respiratory failure,[8] where this strategy is used more commonly for acute exacerbations of chronic obstructive respiratory disease[9-11] and as a bridge to lung transplantation.[12-14] In a systematic review of ECMO without IMV for respiratory failure, the subgroup of patients with ARDS, which included 62 patients from case series (median study sample size of 10 patients), showed the highest failure rate (39.3%).[15] Importantly, failure of ECMO without IMV in ARDS was associated with a high mortality exceeding 50%, highlighting its potential risks and the critical role of patient selection with this strategy.[15-18]

Our primary objective was to analyze patient characteristics, management, complications, and outcomes of 2 distinct strategies of ECMO without IMV strategies, ECMO-PrAw and ECMO-Ext, in a large international cohort of adult ARDS patients.

Methods

Study design

The ECMO-no-VENT-ARDS study is a multicenter, retrospective cohort study conducted in 14 ECMO centers. All participating ICUs obtained institutional ethics committee approval through their local regulations. All procedures in the study were based on the ethical standards of the institutionally responsible committee on human experimentation and the Declaration of Helsinki of 1975, as most recently amended.

The study included adult patients with ARDS treated with ECMO without IMV from January 1, 2015, to April 1, 2024, including ECMO-PrAw and ECMO-Ext. Patients who received ECMO as support for cardiogenic shock, bridge to lung transplantation, or other acute respiratory failure causes other than ARDS were excluded. Follow-up was done until day 90 after ECMO initiation.

Baseline, ECMO, respiratory support, and arterial blood-gas values

We collected age, sex, body mass index, comorbidities, the Sequential Organ-Failure Assessment (SOFA) score, the Simplified Acute Physiology Score II, the Respiratory ECMO Survival Prediction (RESP) score,[19] and the hospital and ICU admission dates. Immunocompromised status was defined as having any of the following: (1) hematological malignancy; (2) active solid tumor; (3) specific antitumor treatment within 1 year; (4) solid-organ transplant; (5) long-term corticosteroids or immunosuppressants; or (6) human immunodeficiency virus infection. Clinical information before ECMO initiation was gathered: (1) ARDS management (neuromuscular blockade, prone position,

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recruitment maneuvers); (2) noninvasive respiratory support (high flow nasal oxygen, noninvasive ventilation); (3) IMV; and (4) IMV settings (mode, positive end-expiratory pressure, FiO_2, respiratory rate, tidal volume, plateau pressure, driving pressure, gas exchange, and routine laboratory values). Ventilatory, gas exchange, and ECMO parameters were also collected at ECMO day 1, ECMO day 3, and ECMO decannulation.

Outcomes

Survival status until 90 days after ECMO initiation was recorded. Cause of death, ICU and hospital survival status, ECMO and IMV duration, and ICU and hospital length of stay were also collected. Extracorporeal membrane oxygenation–related complications and organ dysfunction were included. Major bleeding was defined as requiring ≥ 2 units of packed red blood cells for an obvious hemorrhagic event, necessitating a surgical or interventional procedure, an intracerebral hemorrhage, or any other bleeding leading to death. Failure of the ECMO without IMV strategy was defined as (1) intubation and IMV during ECMO support in the ECMO-PrAw group and (2) reintubation and IMV during ECMO support in the ECMO-Ext group. Causes of ECMO without IMV failure were also recorded.

Statistical analyses

We followed the Strengthening the Reporting of Observational Studies in Epidemiology recommendations for reporting cohort studies.[20] Continuous variables were reported as medians with interquartile ranges (first-third quartiles) and compared using either the Student *t*-test or the Kruskal–Wallis rank sum test, as appropriate. Categorical variables were presented as counts (%) and compared using the Chi-squared or Fisher exact test, depending on the distribution and expected cell counts.

The primary outcome and the effect of each treatment strategy (ie, ECMO-PrAw or ECMO-Ext) were assessed using Kaplan–Meier survival curves and compared using the log-rank test. Baseline characteristics associated with group assignment before ECMO initiation were evaluated using ridge-penalized logistic regression. Variables included in the model were selected a priori based on their anticipated influence on the initial decision to intubate the patient. These variables comprised age, immunocompromised status, pre-ECMO SOFA score, $PaCO_2$, cardiovascular SOFA score, PaO_2/FiO_2 ratio, ICU duration before ECMO, ARDS etiology, and ECMO retrieval status. Ridge penalization was chosen to improve model stability and reduce overfitting while retaining all clinically relevant variables.

Ninety-day mortality risk factors were assessed using a ridge-penalized Cox proportional hazards model with time-dependent covariates, analyzed separately in the ECMO-PrAw and ECMO-Ext cohorts. This approach accounted for temporal variations in patient status and enabled estimation of hazard ratios (HRs) for predefined covariates known to affect ECMO outcomes, including pre-ECMO SOFA score, age, immunocompromised status, and time from ICU admission to ECMO initiation (for the ECMO-PrAw group) or from intubation to IMV weaning (for the ECMO-Ext group). Failure of the respective ECMO-without-IMV strategy was also incorporated into the model as an additional covariate. Ridge penalization was applied to improve coefficient stability, and results were pooled across the 5 imputed datasets. The proportional hazards assumption was checked graphically and using Schoenfeld residuals. To account for potential center-level effects, a sensitivity analysis including the treating center as a random effect was performed.

For the secondary outcome, the cumulative incidence of strategy failure was estimated while accounting for the competing risk of death before intubation or reintubation, depending on the strategy used. Cumulative incidence functions were plotted for each strategy to illustrate the probability of failure over time in the presence of this competing event.

Missing data are described in the corresponding tables. For the analyses, 5 imputed datasets were generated using the mice package, following verification that data were missing completely at random (MCAR) using the mcar package. Multiple imputation was performed accordingly, and all statistical analyses were carried out on the imputed datasets. Results from ridge-penalized models were pooled using Rubin rules.

All analyses were conducted with a 2-sided α level of 0.05. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 4.1.3. The following R packages were used: mice, mcar, survival, and glmnet.

Results

Study population

The study flowchart is presented in Figure 1. Among 27 ECMO centers invited to participate, 13 European (Austria, France, Germany, Italy, Poland, Portugal, and Spain) centers and 1 Latin American (Brazil) center included patients in the ECMO-no-VENT-ARDS study, and 13 centers did not participate (4 did not respond, while 9 did not have patients to include). Of the 14 participating centers, 1 has less than 15 venoarterial or venovenous ECMO cases per year (low volume), 2 have between 15 and 30 cases per year (medium volume), and 11 have more than 30 cases per year (high volume). More detailed information about the participating centers is described in the Supplementary Table 1. Between January 1, 2015, and April 1, 2024, a total of 307 adult ARDS patients treated with a strategy of ECMO without IMV were included: 113 treated with ECMO-PrAw and 194 with ECMO-Ext. In 2023, the ARDS patients treated with ECMO without IMV and included in the study corresponded to 7.0% of the adult patients receiving ECMO for respiratory indications in the 14 participating centers.

Patient characteristics before ECMO

Table 1 and Supplementary Table 2 summarize the key demographic, clinical, and biological characteristics stratified by ECMO treatment strategy and 90-day survival status. Across both the ECMO-PrAw and ECMO-Ext groups, patients were predominantly male (68.7%) and relatively young (median age = 49 years; IQR, 38-58 years). Primary awake ECMO group presented a higher proportion of immunocompromised patients. In the ECMO-PrAw

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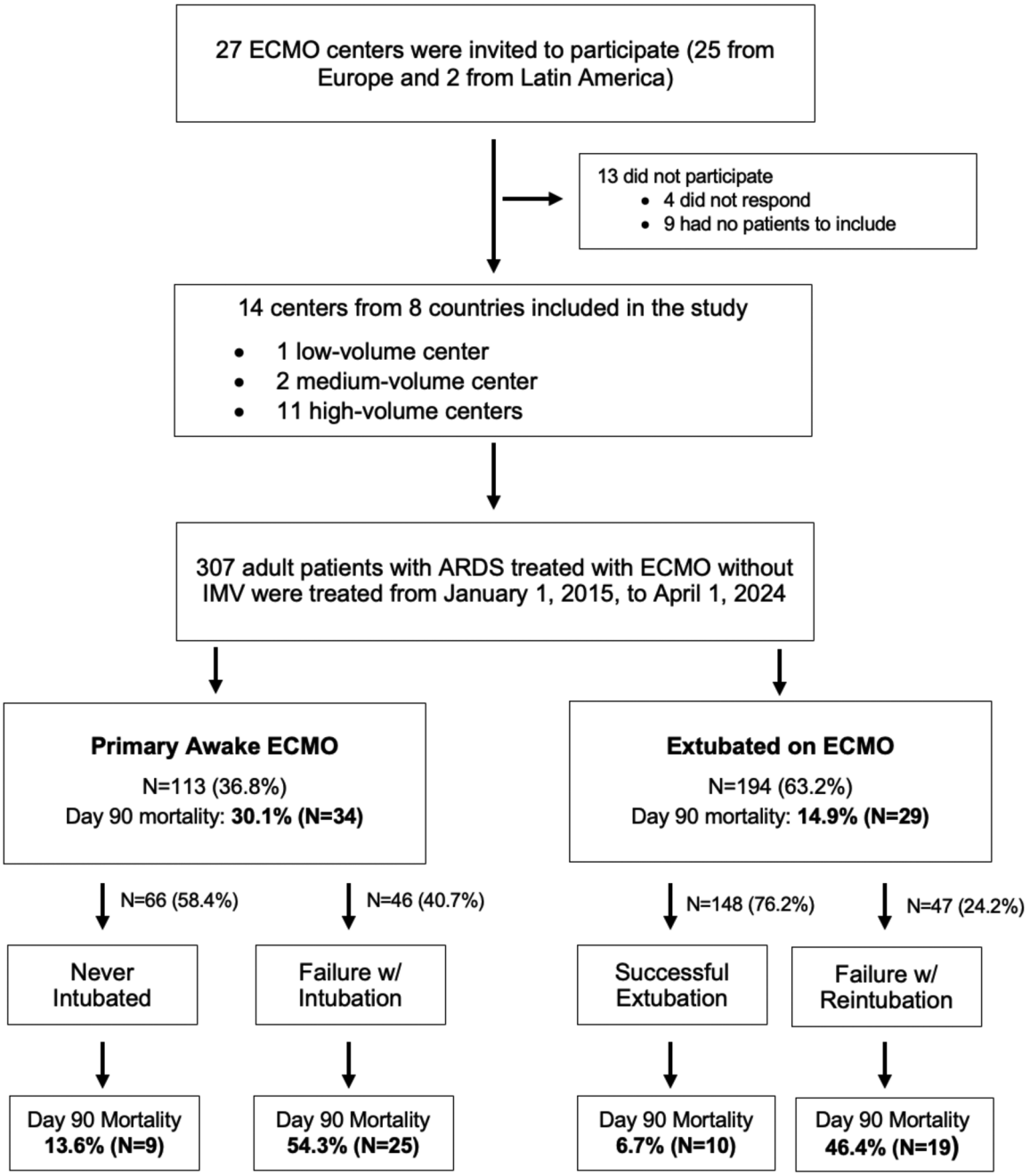


Figure 1 Study flowchart. Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation.

group, chronic pulmonary disease and immunocompromised status were associated with increased mortality. Pulmonary ARDS was the predominant subtype in both groups (96.7%), with viral pneumonia being the leading etiology (58.6%). Severity scores at ICU admission and before ECMO initiation were comparable between survivors and nonsurvivors in both groups, except for the RESP score, which was significantly lower among nonsurvivors in the ECMO-Ext group.

Within the ECMO-PrAw group, nonsurvivors had significantly longer intervals from hospital admission (8 days, IQR = 3-16 days, vs 4 days, IQR = 1-8 days; $P = .005$) and ICU admission (3 days, IQR = 2-4 days, vs 1 day, IQR = 0-3 days; $P < .001$) to ECMO initiation. They also had a longer duration of noninvasive respiratory support before ECMO (3 days, IQR = 2-8 days, vs 2 days, IQR = 1-3 days; $P = .005$). Gas exchange parameters differed significantly between groups: before ECMO initiation, patients in the ECMO-PrAw group had a lower PaO_2/FiO_2 ratio (82, IQR = 63-101 vs 90, IQR = 71-120; $P = .003$), whereas those in the ECMO-Ext group had higher $PaCO_2$ levels (58 mmHg, IQR = 49-72 mmHg, vs 38 mmHg, IQR = 34-45 mmHg; $P < .001$) and a lower pH (7.32, IQR = 7.24-7.38, vs 7.44, IQR = 7.39-7.47; $P < .001$) (Supplementary Table 2).

Extracorporeal membrane oxygenation circuit configurations are detailed in Supplementary Table 3. Extracorporeal membrane oxygenation retrieval, longer time from ICU admission to ECMO initiation (odds ratio [OR] = 1.04; 95% CI, 1.00-1.08), and higher

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Table 1 Demographic and clinical characteristics according to the extracorporeal membrane oxygenation (ECMO) without invasive mechanical ventilation (IMV) treatment strategy and the survival status.

	ECMO-PrAw[a]					ECMO-Ext[a]				
	All	Alive day 90	Dead day 90	*P*-value	No.	All	Alive day 90	Dead day 90	*P*-value	No.
	n = 113	*n* = 79	*n* = 34			*n* = 194	*n* = 165	*n* = 29		
Age, median (IQR), y	49 (38-57)	48 (36-57)	52 (40-60)	.123	113	49 (39-58)	48 (37-56)	58 (52-61)	<.001	194
Gender, No. (%) male	77 (68.1)	52 (65.8)	25 (73.5)	.558	113	134 (69.1)	113 (68.5)	21 (72.4)	.838	194
Hypertension, No. %)	33 (29.2)	22 (27.8)	11 (32.4)	.797	113	54 (27.8)	46 (27.9)	8 (27.6)	1.000	194
Chronic pulmonary disease, No. (%)	30 (26.5)	15 (19.0)	15 (44.1)	.011	113	29 (14.9)	24 (14.5)	5 (17.2)	.770	194
Smoking, No. (%)	14 (12.4)	11 (13.9)	3 (8.82)	.579	113	42 (21.6)	36 (21.8)	6 (20.7)	1.000	194
Diabetes mellitus, No. (%)	17 (15.0)	8 (10.1)	9 (26.5)	.052	113	32 (16.5)	26 (15.8)	6 (20.7)	.587	194
Ischemic cardiopathy, No. (%)	4 (3.54)	3 (3.80)	1 (2.94)	1.000	113	4 (2.06)	2 (1.21)	2 (6.90)	.106	194
Immunocompromised, No. (%)	52 (46.0)	28 (35.4)	24 (70.6)	.001	113	21 (10.8)	18 (10.9)	3 (10.3)	1.000	194
Peripartum, No. (%)	2 (1.77)	2 (2.53)	0 (0.00)	1.000	113	7 (3.61)	7 (4.24)	0 (0.00)	.390	194
Type of ARDS				1.000	113				.141	194
Pulmonary, No. (%)	112 (99.1)	78 (98.7)	34 (100)			185 (95.4)	159 (96.4)	26 (89.7)		
Extrapulmonary, No. (%)	1 (0.88)	1 (1.27)	0 (0.00)			9 (4.64)	6 (3.64)	3 (10.3)		
Cause of ARDS				.255	113				.837	194
Viral pneumonia, No. (%)	69 (61.1)	52 (65.8)	17 (50.0)			111 (57.2)	94 (57.0)	17 (58.6)		
COVID-19, No. (%)	62 (54.9)	48 (60.8)	14 (41.2)			85 (43.8)	71 (43.0)	14 (48.3)		
Bacterial pneumonia, No. (%)	20 (17.7)	13 (16.5)	7 (20.6)			34 (17.5)	30 (18.2)	4 (13.8)		
Other, No. (%)	24 (21.2)	14 (17.7)	10 (29.4)			49 (25.3)	41 (24.8)	8 (27.6)		
SAPS at ICU admission, median (IQR)	29 (23-39)	30 (24-39)	27 (21-37)	.425	111	34 (26-48)	34 (25-48)	37 (28-46)	.869	189
SOFA at ICU admission, median (IQR)	4 (3-6)	4 (3-6)	4 (2-6)	.887	103	7 (4-9)	7 (4-9)	6 (4-8)	.353	193
Pre-ECMO SOFA, median (IQR)	4 (3-7)	4 (3-7)	4 (3-7)	.973	108	6 (4-9)	6 (4-9)	6 (5-8)	.749	190
Pre-ECMO cardiovascular SOFA, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	.959	107	3 (0-3)	3 (0-3)	2 (0-3)	.150	186
RESP score, median (IQR)	3 (1-4)	3 (2-4)	3 (1-4)	.791	89	4 (2-5)	4 (2-5)	3 (2-4)	.033	180
ICU to ECMO, median (IQR), days	1 (0-3)	1 (0-3)	3 (2-4)	<.001	113	4 (1-9)	3 (1-8)	5 (3-9)	.144	194
Hospital to ECMO, median (IQR), days	5 (2-10)	4 (1-8)	8 (3-16)	.005	113	6 (2-12)	6 (2-12)	8 (5-11)	.311	194
ICU to extubation, median (IQR), days	—	—	—	—	—	14 (8-29)	14 (8-29)	14 (8-27)	.922	192
ECMO to extubation, median (IQR), days	—	—	—	—	—	9 (3-19)	9 (4-19)	8 (3-18)	.706	192

(Continued)

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Table 1 Continued.

	ECMO-PrAw[a]					ECMO-Ext[a]				
	All	Alive day 90	Dead day 90	*P*-value	No.	All	Alive day 90	Dead day 90	*P*-value	No.
	n = 113	*n* = 79	*n* = 34			*n* = 194	*n* = 165	*n* = 29		
Pre-ECMO NIRS, median (IQR), days	2 (1-4)	2 (1-3)	3 (2-8)	.005	110	1 (0-3)	1 (0-3)	1 (1-3)	.603	130
Pre-ECMO IMV, median (IQR), days	—	—	—	—	—	2 (1-6)	2 (1-6)	3 (1-4)	.951	191
Pre-ECMO NIRS and IMV, median (IQR), days	—	—	—	—	—	5 (2-11)	5 (2-12)	5 (3-8)	.926	194
Pre-ECMO NMB, No. (%)	—	—	—	—	—	173 (91.1)	149 (92.5)	24 (82.8)	.156	190
Pre-ECMO prone position, No. (%)	—	—	—	—	—	145 (75.9)	124 (76.5)	21 (72.4)	.808	191
Pre-ECMO recruitment maneuvers, No. (%)	—	—	—	—	—	59 (31.1)	53 (32.9)	6 (20.7)	.275	190
ECMO retrieval, No. (%)	14 (12.4)	11 (13.9)	3 (8.82)	.535	113	112 (57.7)	94 (57.0)	18 (62.1)	.757	194

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO-Ext, extubated ECMO; ECMO-PrAw, primary awake ECMO; NIRS, noninvasive respiratory support (encompasses noninvasive ventilation and high-flow oxygen); NMB, neuromuscular blockade; RESP, Respiratory ECMO Survival Prediction score; SAP, Simplified Acute Physiology score; SOFA, Sequential Organ Failure Assessment.
[a]Regarding the "other" ARDS etiologies, in the ECMO-PrAw group, 2 had extrapulmonary sepsis, 6 other causes, and in 16 patients the ARDS etiology was not determined. In the ECMO-Ext group, 9 had lung contusion, 4 extrapulmonary sepsis, 17 other causes, and in 19 patients the ARDS etiology was not determined.

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Table 2 Multivariate logistic regression model including pre-extracorporeal membrane oxygenation (ECMO) variables describing independent associations with group assignment (extubated ECMO vs primary awake ECMO) (imputed datasets).

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1 (0.98-1.02)	.955		
Immunocompromised	0.14 (0.08-0.26)	<.005	0.19 (0.09-0.43)	<.001
SOFA score before ECMO	1.22 (1.12-1.34)	<.005		
Cardiovascular SOFA before ECMO	1.66 (1.4-1.97)	<.005		
$PaCO_2$ before ECMO	1.08 (1.06-1.11)	<.005	1.05 (1.03-1.07)	<.001
PaO_2/FiO_2 before ECMO	3.29 (1.58-6.87)	<.005		
Time from ICU admission to ECMO	1.05 (1.01-1.09)	.014	1.04 (1.00-1.08)	.045
ARDS etiology				
Bacterial pneumonia	Reference		Reference	
Viral pneumonia	0.95 (0.5-1.77)	.863		
Other	1.2 (0.57-2.51)	.627		
ECMO retrieval	9.66 (5.15-18.1)	<.005	7.11 (3.63-13.92)	<.001

Abbreviations: ARDS, acute respiratory distress syndrome; PaO_2/FiO_2, ratio between oxygen partial pressure in arterial blood and the fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

$PaCO_2$ levels before ECMO initiation (OR = 1.05; 95% CI, 1.03-1.07) were associated with assignment to the ECMO-Ext group. In contrast, immunocompromised patients were more likely to receive the ECMO-PrAw strategy (OR = 0.19; 95% CI, 0.09-0.43) (Table 2).

Complications and clinical outcomes

Major bleeding events were common in both the ECMO-PrAw (82.3%) and ECMO-Ext (80.9%) groups; however, hemorrhagic shock was infrequently reported, occurring in only 5 (4.4%) and 8 (4.1%) patients, respectively. In the ECMO-Ext group, ventilator-associated pneumonia was observed in 107 (55.4%) patients, a significantly higher incidence compared to the ECMO-PrAw group (55.4% vs 29.7%; *P* = .006) and was associated with increased mortality (Table 3). Notably, refractory hypoxemia was reported in 20 patients (17.7%) in the ECMO-PrAw group and was similarly associated with higher mortality within this subgroup. Of the patients in ECMO-PrAw who experienced refractory hypoxemia, 13 (65%) were subsequently intubated.

The ECMO-PrAw group experienced a higher 90-day mortality (30.1% vs 14.9%; *P* = .003) compared to the ECMO-Ext group (Supplementary Table 4). Despite similar ECMO duration between groups, the ECMO-Ext cohort had significantly longer ICU and hospital lengths of stay. The principal causes of death in both groups included septic shock, nonspecific multiorgan failure, and persistent respiratory failure (Table 3).

Failure of ECMO without IMV strategy and predictors of 90-day mortality

Strategy failure occurred in 46 (40.7%) patients in the ECMO-PrAw group and 47 (24.2%) patients in the ECMO-Ext group (Figure 2 and Supplementary Figure 1), mostly within the first 10 days (Supplementary Figure 2). The primary reasons for failure were worsening respiratory failure (63.4%), followed by agitation or delirium in the ECMO-PrAw group (30.4%) and inability to clear secretions in the ECMO-Ext group (17.0%) (Supplementary Table 5).

Failure of the ECMO without IMV strategy was associated with a high 90-day mortality: 54.3% in the ECMO-PrAw group and 46.4% in the ECMO-Ext group (*P* = .151) (Figure 2).

In multivariate analysis, strategy failure predicted 90-day mortality in both groups (HR = 8.12; 95% CI, 3.57-18.48; *P* < .001 in ECMO-Ext; HR = 6.40; 95% CI, 2.74-14.91; *P* < .001 in ECMO-PrAw), while higher age (HR = 1.06; 95% CI, 1.03-1.10; *P* = .001) and longer time from ICU admission to ECMO cannulation (HR = 1.05; 95% CI, 1.02-1.08; *P* = .003) were significantly associated with 90-day mortality in ECMO-Ext and ECMO-PrAw, respectively (Table 4). No significant difference in 90-day mortality was observed between early (day 0-1) and delayed (>day 1) strategy failure in either the ECMO-PrAw or ECMO-Ext groups (Supplementary Tables 6 and 7).

Given the high proportion of COVID-19–associated ARDS in our cohort (47.9%), a sensitivity analysis restricted to patients with non–COVID-19–related ARDS was performed. The results were fully concordant with the main findings, with no change in the direction, magnitude, or statistical significance of the association between strategy failure and 90-day mortality (Supplementary Figure 3 and Supplementary Tables 8 and 9). Similarly, a sensitivity analysis including the treating center as a random effect yielded comparable results, confirming a consistent independent association between strategy failure and 90-day mortality (Supplementary Table 10).

Discussion

The present study represents the largest multicenter international cohort of adult ARDS patients treated with ECMO without IMV. Patients selected for ECMO-PrAw and ECMO-Ext presented distinct baseline characteristics, with different strategy failure (40.7% vs 24.2%, respectively) and 90-day mortality (30.1% and 14.9%, respectively) rates. Failure of the ECMO-without-IMV strategy was strongly associated with mortality in both groups, with nearly half of these patients dying by day 90. Age and time from ICU admission to ECMO cannulation were independently associated with mortality in the ECMO-Ext and ECMO-PrAw groups, respectively. Worsening respiratory failure was the main cause of

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Table 3 Clinical outcomes.

	ECMO-PrAw					ECMO-Ext				
	All	Alive day 90	Dead day 90	*P*-value	No.	All	Alive day 90	Dead day 90	*P*-value	No.
	n = 113	*n* = 79	*n* = 34			*n* = 194	*n* = 165	*n* = 29		
Complications, No. (%)										
Major bleeding event	93 (82.3)	65 (82.3)	28 (82.4)	1.000	113	157 (80.9)	138 (83.6)	19 (65.5)	.042	194
Ventilator associated pneumonia	33 (29.7)	21 (27.3)	12 (35.3)	.531	111	107 (55.4)	85 (51.8)	22 (75.9)	.028	193
Bacteriemia	31 (28.7)	21 (28.0)	10 (30.3)	.990	108	49 (26.9)	37 (23.9)	12 (44.4)	.047	182
Deep vein thrombosis	25 (22.3)	23 (29.5)	2 (5.9)	.012	112	52 (26.8)	51 (30.9)	1 (3.4)	.004	194
Refractory hypoxemia	20 (17.7)	7 (8.9)	13 (38.2)	<.001	113	15 (7.7)	12 (7.3)	3 (10.3)	.685	194
Cardiac arrest	5 (4.4)	1 (1.3)	4 (11.8)	.023	113	8 (4.1)	3 (1.8)	5 (17.2)	.004	194
Hemorragic stroke	2 (1.8)	0 (0.0)	2 (5.9)	.091	113	8 (4.1)	3 (1.8)	5 (17.2)	.002	194
Pulmonary embolism	2 (2.0)	2 (2.7)	0 (0.0)	.574	102	6 (3.1)	5 (3.0)	1 (3.4)	1.000	194
Accidental decannulation	3 (2.7)	1 (1.3)	2 (5.9)	.205	113	3 (1.5)	3 (1.8)	0 (0.0)	1.000	194
Ischemic stroke	2 (1.8)	0 (0.0)	2 (5.9)	.077	113	2 (1.0)	2 (1.2)	0 (0.0)	1.000	194
Failure of ECMO-w/o-IMV strategy, No. (%)	46 (40.7)	21 (26.6)	25 (73.5)	<.001	113	47 (24.2)	28 (17.0)	19 (65.5)	<.001	194
ECMO duration, median (IQR), days	17 (9-32)	14 (8-30)	24 (13-38)	.096	113	16 (10-35)	15 (9-33)	23 (16-49)	.016	194
Tracheostomy, No. (%)	38 (33.6)	24 (30.4)	14 (41.2)	.370	113	51 (26.3)	37 (22.4)	14 (48.3)	.007	194
ICU LOS, median (IQR), days	22 (13-43)	19 (12-36)	30 (18-53)	.013	113	33 (18-58)	31 (18-59)	37 (23-51)	.385	194
Hospital LOS, median (IQR), days	37 (25-69)	38 (26-72)	36 (23-64)	.698	113	47 (29-78)	47 (29-81)	41 (28-61)	.244	191
Alive at hospital discharge, No. (%)	72 (63.7)	72 (91.1)	0 (0.00)	<.001	113	153 (78.9)	151 (91.5)	2 (6.90)	<.001	194
Cause of death, No. (%)				—	39				.233	35
Septic shock	16 (41.0)	3 (60.0)	13 (38.2)			6 (17.1)	1 (14.3)	5 (17.9)		
Persistent respiratory failure (non–COVID-19)	8 (20.5)	1 (20.0)	7 (20.6)			9 (25.7)	2 (28.6)	7 (25.0)		
Nonspecific MOF	5 (12.8)	0 (0.00)	5 (14.7)			7 (20.0)	1 (14.3)	6 (21.4)		
Persistent respiratory failure (COVID-19)	5 (12.8)	1 (20.0)	4 (11.8)			3 (8.57)	2 (28.6)	1 (3.57)		
Ictus/neurological damage	2 (5.13)	0 (0.00)	2 (5.88)			4 (11.4)	0 (0.00)	4 (14.3)		
Hemorrhagic shock	2 (5.13)	0 (0.00)	2 (5.88)			2 (5.71)	0 (0.00)	2 (7.14)		
Cardiogenic shock	0 (0.00)	0 (0.00)	0 (0.00)			2 (5.71)	0 (0.00)	2 (7.14)		
Mechanical complications (ECMO circuit)	1 (2.56)	0 (0.00)	1 (2.94)			1 (2.86)	0 (0.00)	1 (3.57)		
Complication during cannulation	0 (0.00)	0 (0.00)	0 (0.00)			1 (2.86)	1 (14.3)	0 (0.00)		

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECMO-Ext, extubated ECMO; ECMO-PrAw, primary awake ECMO; ECMO-w/o-IMV, ECMO without IMV; IMV, invasive mechanical ventilation; LOS, length of stay; MOF, multiple organ failure; SOFA, Sequential Organ Failure Assessment; w/o, without.

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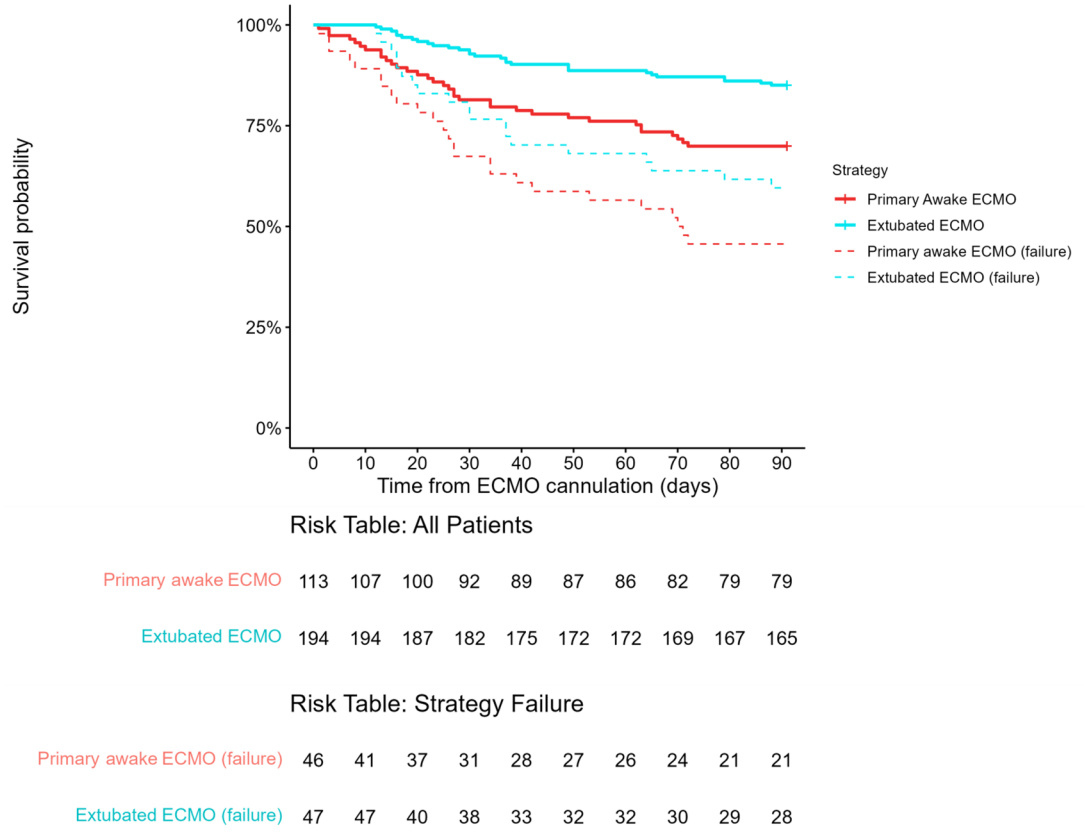


Figure 2 Kaplan–Meier survival curves according to the extracorporeal membrane oxygenation (ECMO) without invasive mechanical ventilation (IMV) strategy.

strategy failure, followed by agitation or delirium in ECMO-PrAw and impaired secretion clearance in ECMO-Ext.

Approximately half of the centers invited to participate in our study did not have adult ARDS patients treated with a strategy of ECMO without IMV. In fact, the ARDS patients included in the study corresponded to a minority (7.0% in 2023) of the adult patients receiving ECMO for respiratory indications in the 14 participating centers. This could be related to the high failure rate reported when using this clinical strategy in this patient subgroup.[7,8,15,17,21,22] In our study, strategy failure after ECMO cannulation in ECMO-PrAw and after extubation in ECMO-Ext occurred mainly within the first 10 days, being lower in the ECMO-Ext group than in the ECMO-PrAw group. Importantly, we could identify that the leading cause of strategy failure was worsening of respiratory failure, followed by agitation/delirium in ECMO-PrAw and inability to clear secretions in ECMO-Ext. Recently, a standardized approach allowed the extubation of 21% of adult ARDS during ECMO support with a strategy failure rate of 20.4%.[1] In this study, extubation during ECMO support was validated by a dedicated intensive care team to exclude major causes of extubation failure, including worsening respiratory failure, impaired secretion clearance, and agitation or delirium. Careful assessment of neuromuscular weakness and respiratory drive before weaning from IMV during ECMO may also help clinicians better identify appropriate candidates.[23] The higher failure rate observed in ECMO-PrAw suggests that patient selection and management for this specific ECMO without IMV strategy are more challenging. Although it has been previously shown to be feasible,[24-26] a study on 18 adult patients with COVID-19 ARDS from 4 German tertiary care ICUs did not support this strategy, as a high rate (78%) of patients were finally intubated,[2] well exceeding the strategy failure rate in our study. Importantly, in this study, the time from ICU admission to ECMO cannulation was longer compared to our cohort (7 vs 1 day), and we demonstrated that the time from ICU admission to ECMO initiation predicted 90-day mortality in the ECMO-PrAw group.

In our cohort, a substantial proportion of patients were immunocompromised (23.8%) or had chronic pulmonary disease (19.2%). The use of ECMO without IMV in these patients may partly reflect the potential to reduce ventilator-induced lung injury and ventilator-associated pneumonia, as they are particularly susceptible to ventilator-related complications and nosocomial infections.[27,28] In addition, the conventional use of ECMO as rescue therapy for ARDS failing IMV remains controversial in these populations.[29,30] Nonetheless, ventilator-associated pneumonia remained a frequent complication in both ECMO-PrAw and ECMO-Ext groups in our study. The use of ECMO without IMV in ARDS was also associated with several ICU- and ECMO-associated complications and major adverse events. Major bleeding events were reported in most patients, underscoring the importance of providing ECMO in centers with extensive experience in the prompt management of ECMO-related complications.[31-33]

We observed a high 90-day mortality among patients who failed ECMO without IMV, particularly in the ECMO-PrAw group (54.3%). This finding is consistent with a recent systematic review of ECMO

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Table 4 Multivariate analysis for 90-day mortality in the primary awake (panel A) and extubated (panel B) extracorporeal membrane oxygenation (ECMO) groups.

Panel A—Primary awake ECMO		
Variable	**Hazard ratio (95% CI)**	***P*-value**
Strategy failure	5.95 (2.63- 13.46)	<.001
Pre-ECMO SOFA	0.90 (0.78, 1.03)	.120
Age	1.02 (0.99-1.06)	.158
ICU-to-ECMO	1.04 (1.01-1.07)	.003
COVID-19	0.56 (0.23-1.39)	.213
Immunocompromised	2.13 (0.85-5.34)	.105
Panel B—extubated ECMO		
Variable	**Hazard ratio (95% CI)**	***P*-value**
Strategy failure	7.67 (3.44-17.11)	<.001
Pre-ECMO SOFA	0.98 (0.86-1.11)	.711
Age	1.06 (1.02-1.10)	<.001
ICU-to-Extubation	1.00 (0.99-1.02)	.758
COVID-19	0.77 (0.35-1.71)	.525
Immunocompromised	0.94 (0.26-3.41)	.922

Abbreviations: ICU-to-extubation, time (in days) from ICU admission to extubation; SOFA, Sequential Organ Failure Assessment.

without IMV for adult respiratory failure, which reported a mortality of 53.8% among ARDS patients in whom this strategy failed.[15] These observations suggest that ECMO without IMV should be restricted to carefully selected ARDS patients, with attention to factors associated with strategy failure as well as predictors of 90-day mortality identified in our study, including older age in ECMO-Ext and longer time from ICU admission to ECMO cannulation in ECMO-PrAw. This consideration is particularly important given that some predictors of strategy failure, such as worsening respiratory failure, agitation or delirium, and impaired secretion clearance, may not yet be apparent when an ECMO-without-IMV strategy is initially pursued. It should be noted, however, that failure of the ECMO-Ext or ECMO-PrAw strategies may represent a dynamic marker of disease progression during ECMO, reflecting the transition from an initial ECMO-without-IMV strategy to a more severe clinical state. In addition, the high mortality observed after strategy failure may also be related to the baseline clinical profile of the patients selected for this approach. In our study, a substantial proportion of patients had significant comorbidities, which were associated with higher mortality in the ECMO-PrAw group. Accordingly, septic shock accounted for a large proportion of deaths (41.0%) in this group.

Future randomized trials in ARDS should compare ECMO strategies without IMV with the conventional approach of weaning IMV only after liberation from ECMO. Our findings suggest that ECMO-PrAw and ECMO-Ext should be evaluated separately, as they involve distinct patient profiles and are associated with different rates of strategy failure and 90-day mortality. Candidate selection will likely be critical, particularly regarding the absence of agitation or delirium and the ability to effectively clear tracheal secretions. Moreover, as a longer delay from ICU admission to ECMO-PrAw initiation was associated with higher 90-day mortality in our study and previous data with delayed initiation reported high rates of subsequent intubation,[2] this strategy may be best considered in patients requiring ECMO early after ICU admission.

Our study has several limitations that need to be addressed. First, no standardized criteria were used to select ARDS patients for ECMO without IMV, which could have created inconsistencies in the outcomes reported by the participant centers. Second, significant differences in ECMO patient management could have occurred between centers and during the period included in the study, which could have significantly impacted the reported ICU and ECMO complication rate. This is particularly relevant given that management of spontaneous breathing in ARDS patients is particularly challenging, with the respiratory effort not always controlled by manipulation of the ECMO sweep gas flow. Moreover, the ventilatory management after extubation (eg, face mask, high-flow oxygen, noninvasive ventilation) in the ECMO-Ext group, which may have influenced the extubation failure rate and patient outcome, was not described and deserves further investigation. Third, our study was conducted mainly in high-volume European ECMO centers, which might limit the generalizability of our results to less experienced centers or other regions of the world. Fourth, our study focused on selected ARDS patients supported with ECMO without IMV (either ECMO-PrAw or ECMO-Ext), which precludes any comparison with patients who received ECMO while on IMV and were managed according to the conventional strategy of weaning ECMO before liberation from IMV. Lastly, potential residual confounding from unmeasured selection factors, importantly limiting the interpretation of adjusted odds and hazard ratios as causal effects, should be acknowledged.

Conclusions

Patients selected for ECMO-PrAw and ECMO-Ext presented distinct baseline characteristics, with different strategy failure and 90-day mortality rates. Strategy failure strongly predicts 90-day mortality in both groups, indicating that these strategies should only be pursued in highly selected ARDS patients. Future randomized studies are needed in ARDS to compare strategies for using ECMO without IMV with the usual practice of weaning from ECMO before liberation from IMV.

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All authors were involved in data generation. M.P., M.S., R.R.A., and T.V. were involved in the data analysis. M.S. and R.R.A. wrote the manuscript. All authors contributed to the revision, read, and approved the final manuscript version. M.S. takes responsibility for the integrity of the work, from inception to the published article.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

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Data availability

Individual patient data reported in this article will be shared after de-identification (text, tables, figures, and appendices), beginning 6 months and ending 2 years after the article publication, to researchers who provide a methodologically sound proposal and after approval of the internal scientific committee. Proposals should be addressed to matthieu.schmidt@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

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